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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,165	12/22/2000	Richard W. Tseng	034827-0302	1234

7590 08/07/2002

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/07/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,165	TSENG ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "real time PCR" in claims 2 and 3. All time is real time, and no definition for this term was found in the specification. Further, all PCR amplification reactions are conducted in real, as opposed to imaginary time.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-6 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mensink et al (British J. Haematol. (August 1998) 102:768-774) in view of Hariharan et al (EMBO J. 6(1):115-119 (1987)) and further in view of Shtivelman (Cell 47:277-284 (1986))

Mensink teaches a method for determining bcr-abl translocation rearrangements for the diagnosis of CML (abstract) comprising the steps of:

a) extracting RNA from a biological sample (page 769, subheading "RNA isolation and cDNA synthesis") and including RNAsin RNAse inhibitor (page 769, column 2),

b) quantifying the extracted RNA by use of PBGD expression (page 770, column 1),

c) reverse transcribing the RNA to cDNA (page 769, column 2),

d) amplifying the cDNA and detecting a cDNA signal using BCR-ABL probes and primers (page 769, column 2),

e) obtaining a standard curve of cDNA signals from serial dilutions of a leukemic cell line, wherein the cDNA is obtained by repeating steps a)-d) with the RNA from the leukemic cell line and not the sample (page 770, subheading "quantitation")

f) extrapolating a measurement of the leukemic cells present in the sample by comparing the signal from step d) with that from step e) (page 770, subheading "quantitation" and page 771, figure 1)

Mensink teaches what he terms "Real Time" detection for steps d) and e) (page 769, column 2).

Mensink teaches that less than a certain amount of BCR-ABL is designated as below detection level and above a certain level is positive (page 770, column 1 last sentence to column 2, first sentence). Mensink teaches that the detection limit is 1 in ten thousand cells (page 770, column 2).

Mensink teaches the normalized dose as a measurment of leukemic cells present in the sample (page 771, table I).

Mensink teaches amplification and detection of the cDNA in a single container (page 769, column 2, subheading "Real Time quanitation using Taqman assay").

Mensink does not teach one of the particular oligonucleotides of SEQ ID NO:s 1-8, but Mensink does teach primer selection "Using the Primer Express software program (Perkin-Elmer, Foster City, Calif. Demo version 1.0 ppd) we designed PCR primers for the amplification of cDNA derived from the BCR-ABL transcript and PBGD transcript (page 769, column 2)".

Hariharan teaches the cDNA sequence for BCR (page 117, figure 2). See alignment below.

```
Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
           chromosome
          Length = 4739

 Score = 38.2 bits (19), Expect = 0.015
 Identities = 19/19 (100%)
 Strand = Plus / Plus


Query: 1    cctcgcagaactcgcaaca 19
             ||||||||||||||||||
Sbjct: 1597 cctcgcagaactcgcaaca 1615



Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
           chromosome
          Length = 4739

 Score = 40.1 bits (20), Expect = 0.012
 Identities = 20/20 (100%)
 Strand = Plus / Plus


Query: 1    gagctgcagatgctgaccaa 20
             ||||||||||||||||||||
Sbjct: 3120 gagctgcagatgctgaccaa 3139
```

Shtivelman teaches the cDNA sequence for ABL (page 278, figures 1 and 2), see alignment below.

```
Human c-abl gene, complete cds
          Length = 3840

 Score = 44.1 bits (22), Expect = 0.001
 Identities = 22/22 (100%)
 Strand = Plus / Minus


Query: 1   tcagaccctgaggctcaaagtc 22
            ||||||||||||||||||||||
Sbjct: 491 tcagaccctgaggctcaaagtc 470
```

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Mensink with the use of functionally equivalent primers selected from the sequences of Hariharan and Shtivelman since Mensink expressly teaches primer selection using commercially available software for BCR-ABL detection from the BCR-ABL published sequences and since Hariharan and Shtivelman provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of BCR-ABL, and in particular for diagnosis of Chronic Myelogenous Leukemia, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

5. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eder et al (Leukemia (September 1999) 13:1383-1389) in view of Hariharan et al (EMBO J. 6(1):115-119 (1987)) and further in view of Shtivelman (Cell 47:277-284 (1986)) and further in view of Ercolani et al (Journal of Biological Chemistry (1988) 263(30):15335-15341).

Eder teaches a method for determining bcr-abl translocation rearrangements for the diagnosis of CML (abstract) comprising the steps of:

a) extracting RNA from a biological sample (page 1384, column 1, subheading "RNA isolation")

b) quantifying the extracted RNA by use of GAPDH expression (page 1384, column 2),

c) reverse transcribing the RNA to cDNA (page 1384, column 1),

d) amplifying the cDNA and detecting a cDNA signal using BCR-ABL probes and primers and GAPDH probes and primers (page 1384, subheading "Realtime PCR"),

e) obtaining a standard curve of cDNA signals from serial dilutions of a leukemic cell line, wherein the cDNA is obtained by repeating steps a)-d) with the RNA from the leukemic cell line such as K562 and not the sample (page 1384, column 2, subheading "normalization and quantitation")

f) extrapolating a measurement of the leukemic cells present in the sample by comparing the signal from step d) with that from step e) (page 1384, column 2 and page 1385, fugre 1).

Eder teaches what he terms "Real Time" detection for steps d) and e) (page 1384, column 1).

Eder teaches the use of the Trizol reagent, which inhibits RNAse activity (page 384, column 1).

Eder runs the cDNA products on an electrophoretic gel to obtain fragment size and identity information (page 1385, figure 1).

Eder teaches that less than a certain amount of BCR-ABL is designated as below detection level and above a certain level is positive (page 1384, column 2). Eder teaches that the detection limit is 1 in ten thousand cells (page 1385, figure 1).

Eder teaches the normalized dose as a measurement of leukemic cells present in the sample (page 1385, table I).

Eder teaches amplification and detection of the cDNA in a single container (page 1384, column 1, subheading "Real Time PCR").

Eder does not teach one of the particular oligonucleotides of SEQ ID NO:s 1-8, but Eder does teach primer selection "Using the Primer Express software version 1.0 (Perkin-Elmer/Applied Biosystems, Foster City, USA) (page 1384, column 1)."

Hariharan teaches the cDNA sequence for BCR (page 117, figure 2). See alignment below.

```
Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
           chromosome
         Length = 4739

 Score = 38.2 bits (19), Expect = 0.015
 Identities = 19/19 (100%)
 Strand = Plus / Plus


Query: 1    cctcgcagaactcgcaaca 19
```

```
            ||||||||||||||||||
Sbjct: 1597 cctcgcagaactcgcaaca 1615


Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
            chromosome
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 Score = 40.1 bits (20), Expect = 0.012
 Identities = 20/20 (100%)
 Strand = Plus / Plus


Query: 1    gagctgcagatgctgaccaa 20
            ||||||||||||||||||||
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```

Shtivelman teaches the cDNA sequence for ABL (page 278, figures 1 and 2), see alignment below.

```
Human c-abl gene, complete cds
          Length = 3840

 Score = 44.1 bits (22), Expect = 0.001
 Identities = 22/22 (100%)
 Strand = Plus / Minus


Query: 1   tcagaccctgaggctcaaagtc 22
           ||||||||||||||||||||||
Sbjct: 491 tcagaccctgaggctcaaagtc 470
```

Ercolan teaches the DNA sequence for GAPDH (page 15340, figure 2) see alignment below.

```
Human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, complete
            cds
          Length = 5378

 Score = 40.1 bits (20), Expect = 0.012
 Identities = 20/20 (100%)
 Strand = Plus / Minus


Query: 1    gaagatggtgatgggatttc 20
            ||||||||||||||||||||
Sbjct: 3407 gaagatggtgatgggatttc 3388
```

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Eder with the use of functionally equivalent primers selected from the sequences of Hariharan, Shtivelman and Ercolani since Eder expressly teaches primer selection using commercially available software for BCR-ABL detection from the BCR-ABL published sequences and since Hariharan, Shtivelman and Ercolani provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of BCR-ABL and GAPDH, and in particular for diagnosis of Chronic Myelogenous Leukemia, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Response to Arguments

6. Applicant's arguments filed June 26, 2002 have been fully considered but they are not persuasive.

With regard to the amendment, this amendment clarifies the use of the oligonucleotides by inserting the word "each of".

Applicant argues that "real time PCR' is well known to those of skill in the art, and that Appendix B shows 383 publications use the term in the title. No such appendix B is found attached to this response. A search of medline identified 213 references which used this term in the title. Taking a deeper look that simply reviewing titles, which gives no information, it is clear that these papers do not use the term to mean the same thing. For example, Aldea et al (J. Clin. Microbiol. (2002) 40(3):1060-1062) use "real time PCR" to refer to detection using the DNA binding dye SYBR Green and light cycler technology. However, Dehee et al (J. Virol. Meth. (2002) 102:37-51) use "real time PCR" to refer to a Taqman assay in which nuclease digestion occurs and is detected in an ABI device. Thus, the two references use different technology, different techniques, different apparatus and share no similiarities but the name. So it is indefinite what technology or limitations are imposed by the term "real time PCR". The examiner notes that these references are not relied upon for the rejection but are simply provided as evidence.

Applicant argues the obviousness rejection. Applicant appears to be arguing an unexpected result of superior detection. This argument is not persuasive for two

reasons. First, no comparative data is presented to demonstrate that the result is, in fact, unexpected. That is, use of the cited prior art method itself in separate experiments might yield equally effective data. Second, with respect to the unexpected results argument itself, applicant's statement is not evidence and the specification lacks comparative data. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Here, the statements regarding any potential unexpected results must be demonstrated, not simply argued by applicant's counsel.

Applicant then argues that there is only an assertion of homology. This is clearly incorrect and Applicant mischaracterizes the rejection. The claimed invention is drawn to detection of a BCR-ABL translocation by selecting primers from BCR and ABL, performing RT PCR, and determining whether a translocation has occurred. The prior art teaches detection of a BCR-ABL translocation by selecting primers from BCR and ABL, performing RT PCR, and determining whether a translocation has occurred. The only significant difference between the prior art and the current claims is the particular primers selected from the BCR and from the ABL sequences. An ordinary practitioner would expect successful detection of the BCR-ABL translocation from every primer selected according to the methodology taught by Eder. Eder expressly teaches computer software to select primers in the BCR and ABL genes to detect translocations

of the BCR-ABL genes as discussed in the rejection above. Thus, the homology is the homology of structure and function. The prior art teaches the same entire structure from which the primers were derived as well as the same function for the primers.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection.

Applicant argues that the particular primers are unobvious because they represent particular members of a class. This is a very small class, made smaller by the ability of a computer to select primers which are preferred within the class. This is an extremely short and defined area for primer selection, particularly when using computer aided selection since one primer must be on one side of the breakpoint and the other primer on the other side of the breakpoint.

Therefore the rejections are maintained.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER
8/4/02